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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| EXAMINER |
|---|
| HABTE, KAHSAY |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1624 | |

DATE MAILED: 03/31/2003

Please find below and/or attached an Office communication concerning this application or proceeding..

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/990,187 | DUGAR ET AL. | |
| | Examiner | Art Unit | |
| | Kahsay Habte, Ph. D. | 1624 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *3/11/03* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-44* is/are pending in the application.

4a) Of the above claim(s) *14,40 and 41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13,15-39 and 42-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

1. Claims 1-44 are pending.

### *Election/Restriction*

2. Applicant's election without traverse of Group IV, Claims 1-13 (in part), 15-38 (in part) and 42-44 (in part) in Paper No. 8 is acknowledged.

### *Objection*

3. Claims 1-13, 15-39 and 42-44 are drawn to multiple inventions for reasons set forth in the restriction requirement. The claims are examined only to the extent that they read on the elected invention. Cancellation of the non-elected subject matter is recommended in response to this Office Action.

### *Claim Rejections - 35 USC § 112*

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 42-44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of most of the diseases, does not reasonably provide enablement for the treatment of CNS injury, stroke or Alzheimer's disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate

in scope with these claims. There has been recited in claim 44 a method of treating stroke, CNS injury or Alzheimer's disease.

A number of factors are relevant to whether undue experimentation would be required to practice the claimed invention, including "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

(1). Breadth of Claims:

(A1). Scope of use (CNS injury) - The scope of use that applicants intend to claim is very broad. It has been recited in claim 60, a method of treating CNS injury. CNS injury is any injury to the central nervous system. The injury can be caused by diseases such as neurological and neurodegenerative disorders or by any physical damage to the CNS system. Disorders of central nervous system disorders include neurological and neurodegenerative disorders. There is no such an agent, which can treat CNS injuries generally. That is because CNS injuries (damage to the CNS system and neurological or neurodegenerative disorders) are extremely varied in origin and nature of effect. For example, the origin and the nature of many neurodegenerative disorders such as Huntington's disease, Pick's disease, Frontotemporal dementia,

Cerebro-Oculo-Facio-Skeletal (COFS) syndrome (cranofacial and skeletal abnormalities), Motor neuron disease (muscle weakness), Corticobasal ganglionic degeneration, Creutzfeldt-Jacob disease (fatal disease), Dementia with Lewy bodies, and Progressive supranuclear palsy Dementia are different one from the other. Other neurological disorders such as Epilepsy, Depression, Anxiety, Meningitis (viral, bacteria, or fungi infection), Encephalitis (viral infection), Rett syndrome, Tinnitus, Narcolepsy, Shy-Drager syndrome, Charcot-Marie-Tooth disease, Tarsal tunnel syndrome, Schizophrenia, Psychosis, Memory loss, Mental retardation, Autism, Migraine, Tension headache, Multiple sclerosis, etc also differ in their origin and nature of effect one from the other. Many neurodegenerative disorders are untreatable to this day. For example, autism and mental retardation are some of the neurological disorders that have no pharmacological treatment.

The symptoms and nature of these diseases are also different one from the other. It can be shown that many of these neurodegenerative disorders have different origin and nature of effect. Some neurodegenerative disorders are hereditary (Charcot-Marie-Tooth disease). Many neurodegenerative disorders vary in how they affect the body and its functions. Diseases such as Cerebral palsy, and Parkinson's disease affect the movement of the patient. Diseases such as Alzheimer's disease affect the memory of the patient.

B. Scope of Compounds - Scope of Compounds - The scope of the compounds is also broad. It is apparent that hundreds of millions of combinations of compounds can be created from the definitions, owing especially to broad scope of Ar, $L^2$, $L^1$, $R^3$, $R^4$, $Z^2$ and $Z^3$.

(2). Direction of Guidance: The amount of direction or guidance is minimal. There is no dosage.

(3). State of Prior Art: There is no evidence of record that compounds structurally similar to these pyridine derivative compounds are in use for the treatment of Alzheimer's disease, stroke, or CNS injury.

(4). Working Examples: There is no any working example that indicates the treatment of conditions (stroke or CNS injury) that are mediated by p38-alpha kinases. There is no data for any actual treatment of disease or of any animal model for treatment of said diseases.

(5). Nature of the Invention and Predictability: It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(6). The Relative Skill of Those in the Art:

CNS (injury)- The skill level is so low that no compound is effective against CNS injury generally. In terms of the neurological or neurodegenerative disorders, this is completely varied. It ranges from areas where the skill level is high, as in tension headache, to autism, where the skill level is so low that there is no effective pharmacological treatment.

Stroke - represents one of the most intractable medical challenges. Stroke is estimated to cause about 15% of deaths, behind only heart disease and cancer. Even those who survive normally suffer from persistent damage, including motor and speech disturbances and/or convulsions. Despite a tremendous effort to resolve these problems, cerebrovascular therapy as so far been limited to trying to prevent further damage in areas on the margins of the ischemic focus, thus trying to maintain adequate perfusion in remaining intact areas, and thereby limit progressive infarction. This is generally done surgically. Standard pharmaceutical treatment, such as antiarrhythmics and antithrombotics don't get at the cause of the stroke or the damage caused, but are mostly done to insure adequate cardiac functioning.

Despite this vast outpouring of research, the skill level in this art is sufficiently low relative to the difficulty of the task that obtaining a neuroprotective treatment of stroke was, as of the filing date, not yet possible. Hence, accomplishing such a goal involves more than routine experimentation. As evidence for this, there is cited Chalmers (TiPS Vol 17, pages 166-172 April 1996), which states flatly on page 170 that, "At present,

there are no effective neuroprotective agents that can clinically ameliorate the effects of stroke in humans." It notes that trials on the use of cytoprotective agents "are ongoing or are planned", clear evidence of the research that remains to be done to determine how to treat stroke. For example, Pentoxifylline has been one of the most intensely studied, with dozens of studies published on its properties. It appears to have a wide variety of effects on leucocytes, erythrocytes, neutrophils, plasma fibrinogen levels. These result in a wide-ranging ability to increase blood flow, resulting in effectiveness in some vascular disorders, especially intermittent claudication. Research with different administration methods, or different subcategories of stroke may well result in the discovery of how to get this drug to work, but the slowness and difficulty of this research shows clearly that this involves undue, not routine experimentation. Applicants' compounds have been subjected to far less study.

Effective acute drug treatment of the stroke itself has so far proved to be beyond the reach of medical science. Major efforts have certainly been pressed in the area of neuroprotective therapeutics. Those studied have included use of Ca antagonists such as Levemopamil and flunarizine, to suppress neuronal calcium influx; NMDA antagonists (both competitive, such as APV and CPP, and non-competitive such as chlorpromazine, ifenprodil and Mg salts) as well as AMPA and kainate antagonists to block post-ischemic receptor-operated calcium channels; attempts to block arachidonic acid cascade or elimination of its metabolic products with agents such as lipogenase inhibitors and thromboxane; use of free oxygen radical scavengers such as superoxide

dismutase, alpha-tocopherol, or allopurinol to inhibit the lipid peroxidation that damages cell membranes, which may indirectly help prevent intracellular calcium overload; anti-edema agents such as corticosteroids; use of 5-$HT_{1A}$ receptor agonists to suppress 5-HT concentrations in the hippocampal extracellular space; use of CRF receptor antagonists to inhibit excitotoxic brain damage; use of serotonin 1A agonists such as ipsapirone, or adenosine modulators such as vinpocetine, to stimulate adenosine, which may act as a protective agent by hyperpolarizing the postsynaptic neuron; use of platelet aggregation inhibitors such as prostacycline and ticlopidine, and other approaches as well.

(7). The Quantity of Experimentation Necessary: Immense, especially in view of points (1) and (6).

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

There has been recited in claim 44 a method of treating Alzheimer's disease, but the specification is not enabled.

A number of factors are relevant to whether undue experimentation would be required to practice the claimed invention, including "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

(1). Breadth of Claims:

Scope of Compounds - The scope of the compounds is also broad. It is apparent that hundreds of millions of combinations of compounds can be created from the definitions, owing especially to broad scope of Ar, $L^2$, $L^1$, $R^3$, $R^4$, $Z^2$ and $Z^3$.

(2). Direction of Guidance: The amount of direction or guidance is minimal. There is no dosage.

(3). State of Prior Art: There is no evidence of record that compounds structurally similar to these pyridine derivative compounds are in use for the treatment of Alzheimer's disease.

(4). Working Examples: There is no any working example that indicates the treatment of Alzheimer's disease that is mediated by p38-alpha kinase. There is no data for any actual treatment of Alzheimer's disease or of any animal model for the treatment of Alzheimer's disease.

(5). Nature of the Invention and Predictability: It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(6). The Relative Skill of Those in the Art: Applicants claim a method of treatment for AD, this is a very hard to treat disease. The central characteristic of Alzheimer's disease is the deficiency in the level of the neurotransmitter Acetylcholine that plays an important role in memory. Alzheimer's Disease is an extraordinarily difficult disease to treat, and has been the subject of a vast amount of research. Despite an enormous number of different approaches, the skill level in the art is so low relative to the difficulty of task that the only success has come from treatment by compounds which are Acetylcholinesterase inhibitors (Aricept®, Cognex®, Exelon®, and Reminyl®) a property these compounds are not disclosed to have.

(7). The Quantity of Experimentation Necessary: Immense, especially in view of point 6, since the inhibition of p38-alpha for the treatment of AD has never been accomplished or even researched. Thus, no guidance from the success of others is available from this experimentation.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

***Claim Rejections - 35 USC § 112***

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 42-44 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In claim 44, there has been recited a method of treating septic shock, but the specification is not enabled.

Septic shock is an acute and serious cardiovascular collapse resulting from the systemic response to an overwhelming bacterial infection. It is manifested by hypotension, a reduced response (or none at all) to vasoconstrictors, generalized tissue damage and multi-organ failure, and involves a severe decrease in systemic vascular resistance and maldistribution of blood flow. All attempts to get an effective treatment of septic shock have failed. Of course, massive doses of antibacterials are given to combat the particular strains of bacteria which have caused the septic shock in the first place. Drugs are given to combat the hypotension, and particular problems resulting from the septic shock are themselves treated (e.g. digitalis for heart failure), but, so far, the septic shock syndrome itself has no treatment.

As further evidence of the low skill level in this area relative to the difficulty of treating the disorder, there is the fact that preclinical testing and even some human testing has proved to be a totally unreliable predictor in this area. The most spectacular example of this was Centoxin (HA-IA or Nebacumab) which had even gotten into some clinical use in Europe before it was withdrawn in 1993. CB006, anti-J5 plasma and methylprednisolone are some other examples of failure in the septic shock treatment. In July 1994, Bradycor failed its Phase II trials and Antril its Phase III trials. This shows that for septic shock, *in vitro* and even a significant amount of *in vivo* testing is not a reliable indicator of actual efficacy.

It should also to be noted that research in this area has focused on the use of monoclonal antibodies; the skill level in the area of treating septic shock with other than monoclonal antibodies would be lower still.

When the best efforts have failed to achieve a goal, it is reasonable for the PTO to require evidence that such a goal has been accomplished, *In re Ferens*, 163 USPQ 609. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs Novo Nordisk*, 42 USPQ2nd 1001, 1006.

***Claim Rejections - 35 USC § 112***

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-13, 15-39 and 42-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention:

a. Claim 1 and claims dependent thereon are rejected because in claim 1 and elsewhere in the claims the phrase "non-interfering substituents" is not clear. What is included and what are not? How can one tell if a substituent is non-interfering or not? What is the effect, if a substituent is a non-interfering one?

b. In claim 1 and elsewhere in the claims, the phrase "$L^1$ and $L^2$ are linkers" is indefinite. What are covered and what are not? It is recommended that applicants recite the linkers in claims 1, 39 and 42.

c. In claims 1 and 39, the phrase "W and X is a spacer" is indefinite. What is included and what is not?

d. In claim 39, the phrase "for treating conditions characterized enhanced p38-α activity" is not clear. Is this a composition claim or a method claim? If it is a method claim, then it should be written as a method claim language. If it is a composition claim, then said phrase should be removed. Normally, a composition claim is written as "A pharmaceutical composition of compounds of formula (1) and pharmaceutically acceptable carrier."

d. In claim 42, there has been recited a method to treat a condition mediated by p38-α kinase. The scope of claim 57 is unknown. Which diseases are these? Determining whether a given disease responds or does not respond to such mediator will surely involve undue experimentation. Suppose that a given inhibitor "compound X" when administered to a patient with Disease D does not obtain a response. Does one then conclude that Disease D does not fall within this claim? Keep in mind that:

A. It may be that the next patient will respond. It is quite common for pharmaceuticals to work only with some people, not all. Thus, how many need to be tested?

B. It may be that the wrong dosage or dosage regimen was employed. It is quite common for pharmaceuticals to work at one dosage, but not at another which is

significantly higher or lower. Furthermore, the dosage regimen may be vital --- should the drug be given e.g. once a day, or four times in divided dosages? Thus, how many dosages and dosage regimens must be tried before one is certain that this pharmaceutical won't affect Disease D?

C. It may be that X simply isn't potent enough for Disease D, but that another inhibitor Y is potent enough, so that D really does fall within the claim. Thus, how many different mediators must be tried before one concludes that D doesn't fall within the claim?

D. Conversely, if D responds to Y but not to X, can one really conclude that D falls within the claim? It may be that the X result is giving the accurate answer, and that the success of Y arises from some other unknown property which Y is capable of. Thus, when mixed results are obtained, how many more pharmaceuticals need be tested?

E. Finally, suppose that X really will work, but only when combined with Z. There are for example, agents in the antiviral and anticancer technology which are not themselves effective, but the disease will respond when the agents are combined with something else.

F. In addition, literally speaking, any disorder can be treated with any drug, although the treatment might not be successful. Assuming that "successful treatment" is what is intended, what criterion is to be used? If one person in 10 responds to a given drug, does that mean that the disease is treatable? One in 100? 1,000? 10,000?

As a result, determining the true scope of the claim will involve extensive and potentially open-ended research. Without it, one skilled in the art cannot determine the actual scope of the claim. Hence, the claim is indefinite.

***Conclusion***

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kahsay Habte, Ph. D. whose telephone number is (703) 308-4717. The examiner can normally be reached on M-F (9.00AM- 5:30PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund Shah can be reached on 703-308-4716. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Kahsay Habte, Ph. D.
Examiner
Art Unit 1624

KH
March 28, 2003

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